ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 6,000 units
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenecteplase Boehringer Ingelheim Pharma KG 6,000 units
1 vial contains 6,000 units (30 mg) tenecteplase.
1 prefilled syringe contains 6 ml water for injections.

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a recombinant fibrin-specific plasminogen activator.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The reconstituted preparation results in a colourless to pale yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenecteplase Boehringer Ingelheim Pharma KG is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Tenecteplase Boehringer Ingelheim Pharma KG should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with Tenecteplase Boehringer Ingelheim Pharma KG should be initiated as soon as possible after onset of symptoms.

Tenecteplase Boehringer Ingelheim Pharma KG should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10
See section 6.6.: Instructions for use and handling			

The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line may be used for administration of Tenecteplase Boehringer Ingelheim Pharma KG in 0.9% sodium chloride solution only. Tenecteplase Boehringer Ingelheim Pharma KG is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution.

Adjunctive therapy
Acetylsalicylic acid (ASA) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

ASA should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The ASA dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

4.3 Contraindications

Tenecteplase Boehringer Ingelheim Pharma KG is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis

- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

4.4 Special warnings and special precautions for use

Bleeding

The most common complication encountered during Tenecteplase Boehringer Ingelheim Pharma KG therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Tenecteplase Boehringer Ingelheim Pharma KG therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with Tenecteplase Boehringer Ingelheim Pharma KG.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. The use of Tenecteplase Boehringer Ingelheim Pharma KG therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Tenecteplase Boehringer Ingelheim Pharma KG is administered.

GPIIb/IIIa antagonists

There is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration

Since at present there is no experience with re-administration of Tenecteplase Boehringer Ingelheim Pharma KG, the re-administration is not recommended. However, no antibody formation to the tenecteplase molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case, tenecteplase should

not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Tenecteplase Boehringer Ingelheim Pharma KG and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with Tenecteplase Boehringer Ingelheim Pharma KG.

Medicinal products that affect coagulation or those that alter platelet function (e.g. ticlopidine, clopidogrel, LMWH) may increase the risk of bleeding prior to, during or after Tenecteplase Boehringer Ingelheim Pharma KG therapy.

4.6 Pregnancy and lactation

No experience in pregnant women is available for tenecteplase. Because animal studies (see also section 5.3.) have shown a high risk of vaginal bleeding presumably from the placenta and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

It is not known if tenecteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Haemorrhage
Haemorrhage is a common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Occasionally, (< 10%) gastro-intestinal or genitourinary bleeding and epistaxis occurred. Haemopericardium, retroperitoneal bleedings and cerebral haemorrhage were rarely observed (< 1%). Blood transfusions were rarely required.

Cardiovascular
As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- common (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare (>0.01%, <0.1%): pulmonary embolism

These cardiovascular events can be life-threatening and may lead to death.

Tenecteplase Boehringer Ingelheim Pharma KG therapy may lead to crystal cholesterol embolisation or thrombotic embolism in very rare cases.

Anaphylactoid Reaction
Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other
Nausea and/or vomiting and fever were commonly reported and are most frequent of the remaining adverse events.

4.9 Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets), see also section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, ATC code: B01A D

Mechanism of action
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects
After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Clinical effects
Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

A large scale mortality trial (ASSENT II) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs. 28.9%, p=0.0003). This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, p=0.0002). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labeled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to what extent tenecteplase binds to plasma proteins in humans.

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half life is 24 ± 5.5 (mean +/-SD) min, which is 5 times longer than native t-PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

The effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known. There is no specific experience to guide the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency. However, based on animal data it is not expected that renal dysfunction will affect the pharmacokinetics.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by changes of ECG, but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was limited to an embryotoxicity study in rabbits, as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: L-arginine, phosphoric acid, polysorbate 20.
Solvent: water for injections

6.2 Incompatibilities

Tenecteplase Boehringer Ingelheim Pharma KG is incompatible with dextrose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30° C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C.

6.4 Special precautions for storage

Do not store above 30° C. Keep the container in the outer carton.

6.5 Nature and contents of container

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.
10 ml polypropylene syringe pre-filled with 6 ml of water for injections for reconstitution.

6.6 Instructions for use and handling, and disposal

Tenecteplase Boehringer Ingelheim Pharma KG should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (ml)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6,000	30
≥ 60 to < 70	7	7,000	35
≥ 70 to < 80	8	8,000	40
≥ 80 to < 90	9	9,000	45
≥ 90	10	10,000	50

2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Place the vial on a firm surface and strongly press down the body of the syringe until a ***"click"*** is noticed. The ***"click"*** confirms the system is activated. Check carefully there is no leakage of fluid. Failure to complete these steps correctly may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.
5. Add the water for injections into the vial by pushing the syringe plunger slowly down to avoid foaming.
6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Withdraw into the syringe the appropriate volume of reconstituted solution of Tenecteplase Boehringer Ingelheim Pharma KG, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Tenecteplase Boehringer Ingelheim Pharma KG is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2001

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 8,000 units
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenecteplase Boehringer Ingelheim Pharma KG 8,000 units
1 vial contains 8,000 units (40 mg) tenecteplase.
1 prefilled syringe contains 8 ml water for injections.

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a recombinant fibrin-specific plasminogen activator.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The reconstituted preparation results in a colourless to pale yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenecteplase Boehringer Ingelheim Pharma KG is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Tenecteplase Boehringer Ingelheim Pharma KG should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with Tenecteplase Boehringer Ingelheim Pharma KG should be initiated as soon as possible after onset of symptoms.

Tenecteplase Boehringer Ingelheim Pharma KG should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
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≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10
see section 6.6.: Instructions for use and handling			

The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line may be used for administration of Tenecteplase Boehringer Ingelheim Pharma KG in 0.9% sodium chloride solution only. Tenecteplase Boehringer Ingelheim Pharma KG is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution.

Adjunctive therapy
Acetylsalicylic acid (ASA) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

ASA should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The ASA dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

4.3 Contraindications

Tenecteplase Boehringer Ingelheim Pharma KG is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis

- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

4.4 Special warnings and special precautions for use

Bleeding

The most common complication encountered during Tenecteplase Boehringer Ingelheim Pharma KG therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Tenecteplase Boehringer Ingelheim Pharma KG therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with Tenecteplase Boehringer Ingelheim Pharma KG.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. The use of Tenecteplase Boehringer Ingelheim Pharma KG therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Tenecteplase Boehringer Ingelheim Pharma KG is administered.

GPIIb/IIIa antagonists

There is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration

Since at present there is no experience with re-administration of Tenecteplase Boehringer Ingelheim Pharma KG, the re-administration is not recommended. However, no antibody formation to the tenecteplase molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case, tenecteplase should

not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Tenecteplase Boehringer Ingelheim Pharma KG and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with Tenecteplase Boehringer Ingelheim Pharma KG.

Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding prior to, during or after Tenecteplase Boehringer Ingelheim Pharma KG therapy.

4.6 Pregnancy and lactation

No experience in pregnant women is available for tenecteplase. Because animal studies (see also section 5.3.) have shown a high risk of vaginal bleeding presumably from the placenta and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

It is not known if tenecteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Haemorrhage
Haemorrhage is a common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Occasionally, (< 10%) gastro-intestinal or genitourinary bleeding and epistaxis occurred. Haemopericardium, retroperitoneal bleedings and cerebral haemorrhage were rarely observed (< 1%). Blood transfusions were rarely required.

Cardiovascular
As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- common (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare (>0.01%, <0.1%): pulmonary embolism

These cardiovascular events can be life-threatening and may lead to death.

Tenecteplase Boehringer Ingelheim Pharma KG therapy may lead to crystal cholesterol embolisation or thrombotic embolism in very rare cases.

Anaphylactoid Reaction
Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other
Nausea and/or vomiting and fever were commonly reported and are most frequent of the remaining adverse events.

4.9 Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets), see also section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, ATC code: B01A D

Mechanism of action
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects
After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Clinical effects
Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

A large scale mortality trial (ASSENT II) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs. 28.9%, p=0.0003). This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, p=0.0002). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labeled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to what extent tenecteplase binds to plasma proteins in humans.

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half life is 24 ± 5.5 (mean

+/-SD) min, which is 5 times longer than native t-PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

The effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known. There is no specific experience to guide the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency. However, based on animal data it is not expected that renal dysfunction will affect the pharmacokinetics.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by changes of ECG, but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was limited to an embryotoxicity study in rabbits as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: L-arginine, phosphoric acid, polysorbate 20.
Solvent: water for injections

6.2 Incompatibilities

Tenecteplase Boehringer Ingelheim Pharma KG is incompatible with dextrose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30° C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C.

6.4 Special precautions for storage

Do not store above 30° C. Keep the container in the outer carton.

6.5 Nature and contents of container

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.
10 ml polypropylene syringe pre-filled with 8 ml of water for injections for reconstitution.

6.6 Instructions for use and handling, and disposal

Tenecteplase Boehringer Ingelheim Pharma KG should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (ml)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6,000	30
≥ 60 to < 70	7	7,000	35
≥ 70 to < 80	8	8,000	40
≥ 80 to < 90	9	9,000	45
≥ 90	10	10,000	50

2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Place the vial on a firm surface and strongly press down the body of the syringe until a ***"click"*** is noticed. The ***"click"*** confirms the system is activated. Check carefully there is no leakage of fluid. Failure to complete these steps correctly may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.
5. Add the water for injections into the vial by pushing the syringe plunger slowly down to avoid foaming.
6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Withdraw into the syringe the appropriate volume of reconstituted solution of Tenecteplase Boehringer Ingelheim Pharma KG, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Tenecteplase Boehringer Ingelheim Pharma KG is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2001

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 10,000 units
Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenecteplase Boehringer Ingelheim Pharma KG 10,000 units
1 vial contains 10,000 units (50 mg) tenecteplase.
1 prefilled syringe contains 10 ml water for injections.

The reconstituted solution contains 1,000 units (5 mg) tenecteplase per ml.

Potency of tenecteplase is expressed in units (U) by using a reference standard which is specific for tenecteplase and is not comparable with units used for other thrombolytic agents.

Tenecteplase is a recombinant fibrin-specific plasminogen activator.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The reconstituted preparation results in a colourless to pale yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenecteplase Boehringer Ingelheim Pharma KG is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

4.2 Posology and method of administration

Tenecteplase Boehringer Ingelheim Pharma KG should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Treatment with Tenecteplase Boehringer Ingelheim Pharma KG should be initiated as soon as possible after onset of symptoms.

Tenecteplase Boehringer Ingelheim Pharma KG should be administered on the basis of body weight, with a maximum dose of 10,000 units (50 mg tenecteplase). The volume required to administer the correct dose can be calculated from the following scheme:

Patients' body weight category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding volume of reconstituted solution (ml)
< 60	6,000	30	6
≥ 60 to < 70	7,000	35	7
≥ 70 to < 80	8,000	40	8
≥ 80 to < 90	9,000	45	9
≥ 90	10,000	50	10
see section 6.6.: Instructions for use and handling			

The required dose should be administered as a single intravenous bolus over approximately 10 seconds.

A pre-existing intravenous line may be used for administration of Tenecteplase Boehringer Ingelheim Pharma KG in 0.9% sodium chloride solution only. Tenecteplase Boehringer Ingelheim Pharma KG is incompatible with dextrose solution.

No other medicinal product should be added to the injection solution.

Adjunctive therapy
Acetylsalicylic acid (ASA) and heparin should be administered as soon as possible after diagnosis to inhibit the thrombogenic process.

ASA should be administered as soon as possible after AMI symptom onset and continued as long-term treatment. The recommended initial oral dose is between 150 and 325 mg per day. If the patient is unable to ingest tablets, an initial dose of 100-250 mg may be given intravenously if available. The ASA dosage during the following days will be at the discretion of the treating physician.

Heparin should be administered as soon as possible after the diagnosis of AMI has been confirmed, and continued for at least 48 hours on a body weight adjusted basis. For patients weighing 67 kg or less, an initial intravenous heparin bolus not exceeding 4,000 IU is recommended followed initially by not more than an 800 IU/hour infusion. For patients weighing more than 67 kg, an initial intravenous heparin bolus not exceeding 5,000 IU is recommended followed initially by not more than 1,000 IU/hour infusion. For patients already receiving heparin treatment, the initial bolus should not be given. The infusion rate should be adjusted to maintain an aPTT of 50-75 seconds (1.5 to 2.5 times control or a heparin plasma level of 0.2 to 0.5 IU/ml).

4.3 Contraindications

Tenecteplase Boehringer Ingelheim Pharma KG is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding:

- Significant bleeding disorder either at present or within the past 6 months
- Patients with current concomitant oral anticoagulant therapy (INR > 1.3)
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Known haemorrhagic diathesis
- Severe uncontrolled hypertension
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months
- (this includes any trauma associated with the current AMI)
- Recent trauma to the head or cranium
- Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
- Acute pericarditis and/or subacute bacterial endocarditis
- Acute pancreatitis

- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Active peptic ulceration
- Arterial aneurysm and known arterial/venous malformation
- Neoplasm with increased bleeding risk
- Any known history of stroke or transient ischaemic attack or dementia
- Hypersensitivity to the active substance tenecteplase and to any of the excipients

4.4 Special warnings and special precautions for use

Bleeding

The most common complication encountered during Tenecteplase Boehringer Ingelheim Pharma KG therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Tenecteplase Boehringer Ingelheim Pharma KG therapy, bleeding from recent puncture site may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheters as well as intramuscular injections and non-essential handling of the patient should be avoided during treatment with Tenecteplase Boehringer Ingelheim Pharma KG.

Most frequently haemorrhage at the injection site, and occasionally genitourinary and gingival bleeding were observed.

Should serious bleeding occur, in particular cerebral haemorrhage, concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative. The use of Tenecteplase Boehringer Ingelheim Pharma KG therapy has to be carefully evaluated in order to balance the potential risks with anticipated benefits under the following conditions:

- Systolic blood pressure > 160 mm Hg
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within the past 10 days)
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Any known recent (within the past 2 days) intramuscular injection
- Advanced age, i.e. over 75 years
- Low body weight < 60 kg

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (pacemaker, defibrillator) be available when Tenecteplase Boehringer Ingelheim Pharma KG is administered.

GPIIb/IIIa antagonists

There is no experience with the use of GPIIb/IIIa antagonists within the first 24 hours after start of treatment.

Re-administration

Since at present there is no experience with re-administration of Tenecteplase Boehringer Ingelheim Pharma KG, the re-administration is not recommended. However, no antibody formation to the tenecteplase molecule has been observed. If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated. In any case, tenecteplase should

not be re-administered before assessment of haemostatic factors like fibrinogen, plasminogen and alpha2-antiplasmin.

4.5. Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Tenecteplase Boehringer Ingelheim Pharma KG and medicinal products commonly administered in patients with AMI have been performed. However, the analysis of data from more than 12,000 patients treated during phase I, II and III did not reveal any clinically relevant interactions with medicinal products commonly used in patients with AMI and concomitantly used with Tenecteplase Boehringer Ingelheim Pharma KG.

Medicinal products that affect coagulation or those that alter platelet function (e.g. ticlopidine, clopidogrel, LMWH) may increase the risk of bleeding prior to, during or after Tenecteplase Boehringer Ingelheim Pharma KG therapy.

4.6 Pregnancy and lactation

No experience in pregnant women is available for tenecteplase. Because animal studies (see also section 5.3.) have shown a high risk of vaginal bleeding presumably from the placenta and of pregnancy loss, the benefit of treatment has to be evaluated against the potential risks which may aggravate an acute life-threatening situation.

It is not known if tenecteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Haemorrhage
Haemorrhage is a common undesirable effect associated with the use of tenecteplase. The type of haemorrhage is predominantly superficial at the injection site. Ecchymoses are observed commonly but usually do not require any specific action. Occasionally, (< 10%) gastro-intestinal or genitourinary bleeding and epistaxis occurred. Haemopericardium, retroperitoneal bleedings and cerebral haemorrhage were rarely observed (< 1%). Blood transfusions were rarely required.

Cardiovascular
As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common (>10%): hypotension, heart rate and rhythm disorders, angina pectoris
- common (>1%, <10%): recurrent ischaemia, heart failure, reinfarction, cardiogenic shock, pericarditis, pulmonary oedema
- uncommon (>0.1%, <1%): cardiac arrest, mitral insufficiency, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupturerare (>0.01%, <0.1%): pulmonary embolism

These cardiovascular events can be life-threatening and may lead to death.

Tenecteplase Boehringer Ingelheim Pharma KG therapy may lead to crystal cholesterol embolisation or thrombotic embolism in very rare cases.

Anaphylactoid Reaction
Anaphylactoid reactions (e.g. rash, urticaria, laryngeal oedema) have been rarely reported.

Other
Nausea and/or vomiting and fever were commonly reported and are most frequent of the remaining adverse events.

4.9 Overdose

In the event of overdose there may be an increased risk of bleeding. In case of severe prolonged bleeding substitution therapy may be considered (plasma, platelets), see also section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, ATC code: B01A D

Mechanism of action
Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

Pharmacodynamic effects
After administration of tenecteplase dose dependent consumption of α2-antiplasmin (the fluid-phase inhibitor of plasmin) with consequent increase in the level of systemic plasmin generation have been observed. This observation is consistent with the intended effect of plasminogen activation. In comparative studies a less than 15% reduction in fibrinogen and a less than 25% reduction in plasminogen were observed in subjects treated with the maximum dose of tenecteplase (10,000 U, corresponding to 50 mg), whereas alteplase caused an approximately 50% decrease in fibrinogen and plasminogen levels. No clinically relevant antibody formation was detected at 30 days.

Clinical effects
Patency data from the phase I and II angiographic studies suggest that tenecteplase, administered as a single intravenous bolus, is effective in dissolving blood clots in the infarct-related artery of subjects experiencing an AMI on a dose related basis.

A large scale mortality trial (ASSENT II) in approx. 17,000 patients showed that tenecteplase is therapeutically equivalent to alteplase in reducing mortality (6.2% for both treatments, at 30 days, upper limit of the 95% CI for the relative risk ratio 1.124) and that the use of tenecteplase is associated with a significantly lower incidence of non-intracranial bleedings (26.4% vs. 28.9%, p=0.0003). This translates into a significantly lower need of transfusions (4.3% vs. 5.5%, p=0.0002). Intracranial haemorrhage occurred at a rate of 0.93% vs. 0.94% for tenecteplase and alteplase, respectively.

Coronary patency and limited clinical outcome data showed that AMI patients have been successfully treated later than 6 hours after symptom onset.

5.2 Pharmacokinetic properties

Tenecteplase is an intravenously administered, recombinant protein that activates plasminogen. Tenecteplase is cleared from circulation by binding to specific receptors in the liver followed by catabolism to small peptides. Binding to hepatic receptors is, however, reduced compared to native t-PA, resulting in a prolonged half-life. Data on tissue distribution and elimination were obtained in studies with radioactively labeled tenecteplase in rats. The main organ to which tenecteplase distributed was the liver. It is not known whether and to what extent tenecteplase binds to plasma proteins in humans.

After single intravenous bolus injection of tenecteplase in patients with acute myocardial infarction, tenecteplase antigen exhibits biphasic elimination from plasma. There is no dose dependence of tenecteplase clearance in the therapeutic dose range. The initial, dominant half life is 24 ± 5.5 (mean

+/-SD) min, which is 5 times longer than native t PA. The terminal half-life is 129 ± 87 min, and plasma clearance is 119 ± 49 ml/min.

Increasing body weight resulted in a moderate increase of tenecteplase clearance, and increasing age resulted in a slight decrease of clearance. Women exhibit in general lower clearance than men, but this can be explained by the generally lower body weight of women.

The effect of renal and hepatic dysfunction on pharmacokinetics of tenecteplase in humans is not known. There is no specific experience to guide the adjustment to tenecteplase dose in patients with hepatic and severe renal insufficiency. However, based on animal data it is not expected that renal dysfunction will affect the pharmacokinetics.

5.3 Preclinical safety data

Intravenous single dose administration in rats, rabbits and dogs resulted only in dose-dependent and reversible alterations of the coagulation parameters with local haemorrhage at the injection site, which was regarded as a consequence of the pharmacodynamic effect of tenecteplase. Multiple-dose toxicity studies in rats and dogs confirmed these above-mentioned observations, but the study duration was limited to two weeks by antibody formation to the human protein tenecteplase, which resulted in anaphylaxis.

Safety pharmacology data in cynomolgus monkeys revealed reduction of blood pressure followed by changes of ECG, but these occurred at exposures that were considerably higher than the clinical exposure.

With regard to the indication and the single dose administration in humans, reproductive toxicity testing was limited to an embryotoxicity study in rabbits, as a sensitive species. Tenecteplase induced total litter deaths during the mid-embryonal period. When tenecteplase was given during the mid- or late-embryonal period maternal animals showed vaginal bleeding on the day after the first dose. Secondary mortality was observed 1-2 days later. Data on the foetal period are not available.

Mutagenicity and carcinogenicity are not expected for this class of recombinant proteins and genotoxicity and carcinogenicity testing were not necessary.

No local irritation of the blood vessel was observed after intravenous, intra-arterial or paravenous administration of the final formulation of tenecteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: L-arginine, phosphoric acid, polysorbate 20.
Solvent: water for injections

6.2 Incompatibilities

Tenecteplase Boehringer Ingelheim Pharma KG is incompatible with dextrose infusion solutions.

6.3 Shelf life

Shelf life as packaged for sale
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30° C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C.

6.4 Special precautions for storage

Do not store above 30° C. Keep the container in the outer carton.

6.5 Nature and contents of container

20 ml glass vial type I, with a coated (B2-42) grey rubber stopper and a vial cap with integrated reconstitution device of polyethylene filled with powder for solution for injection.
10 ml polypropylene syringe pre-filled with 10 ml of water for injections for reconstitution.

6.6 Instructions for use and handling, and disposal

Tenecteplase Boehringer Ingelheim Pharma KG should be reconstituted by adding the complete volume of water for injections from the pre-filled syringe to the vial containing the powder for injection.

1. Ensure that the appropriate vial size is chosen according to the body weight of the patient.

Patients' body weight category (kg)	Volume of reconstituted solution (ml)	Tenecteplase (U)	Tenecteplase (mg)
< 60	6	6,000	30
≥ 60 to < 70	7	7,000	35
≥ 70 to < 80	8	8,000	40
≥ 80 to < 90	9	9,000	45
≥ 90	10	10,000	50

2. Check that the cap of the vial is still intact.
3. Remove the vial cap and connect immediately the pre-filled-syringe to the Luer lock of the Bioset.
4. Place the vial on a firm surface and strongly press down the body of the syringe until a ***"click"*** is noticed. The ***"click"*** confirms the system is activated. Check carefully there is no leakage of fluid. Failure to complete these steps correctly may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.
5. Add the water for injections into the vial by pushing the syringe plunger slowly down to avoid foaming.
6. Reconstitute by swirling gently.
7. The reconstituted preparation results in a colourless to pale yellow, clear solution. Only clear solution without particles should be used.
8. Directly before the solution will be administered, invert the vial with the syringe still attached, so that the syringe is below the vial.
9. Withdraw into the syringe the appropriate volume of reconstituted solution of Tenecteplase Boehringer Ingelheim Pharma KG, based on the patient's weight.
10. Disconnect the syringe from the vial.
11. Tenecteplase Boehringer Ingelheim Pharma KG is to be administered to the patient, intravenously in about 10 seconds. It should not be administered in a line containing dextrose.
12. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2001

10. DATE OF REVISION OF THE TEXT

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT
Tenecteplase Boehringer Ingelheim Pharma KG 6,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)
6,000 U tenecteplase per vial

When reconstituted with 6 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS
Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS
1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION
For intravenous use after reconstitution with 6 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.

8. EXPIRY DATE
EXP {month/year}

9. SPECIAL STORAGE CONDITIONS
Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/001

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

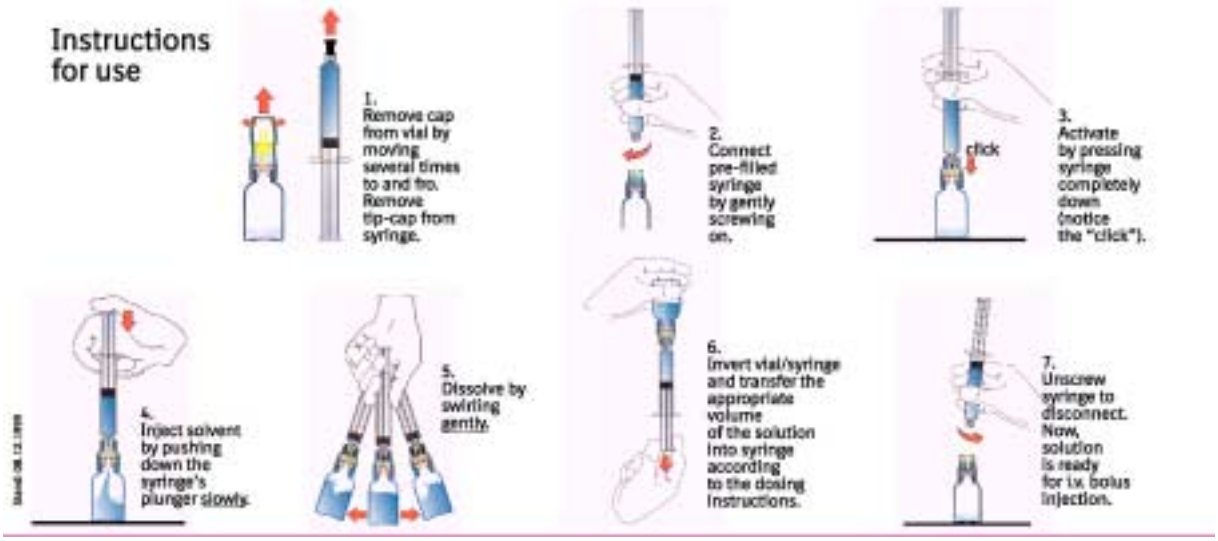
15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM

Step 3:
Place the vial on a firm surface and strongly press down the body of the syringe until an evident ***"click"*** is noticed. The ***"click"*** confirms the system is activated.

Below "Instructions for use"
Failure to complete step 3 correctly may lead to leakage of fluid and greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.



PARTICULARS TO APPEAR ON THE VIAL LABEL

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 6,000 U
Powder for solution for injection.
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

6,000 U tenecteplase per vial

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 6 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Read the package leaflet before use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for Tenecteplase Boehringer Ingelheim Pharma KG 6,000 U
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

Reconstituted solution, for patients of body weight (kg):

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 ml water for injections

PARTICULARS TO APPEAR ON THE CARTON LABEL.

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 8,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

8,000 U tenecteplase per vial

When reconstituted with 8 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 8 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/002

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

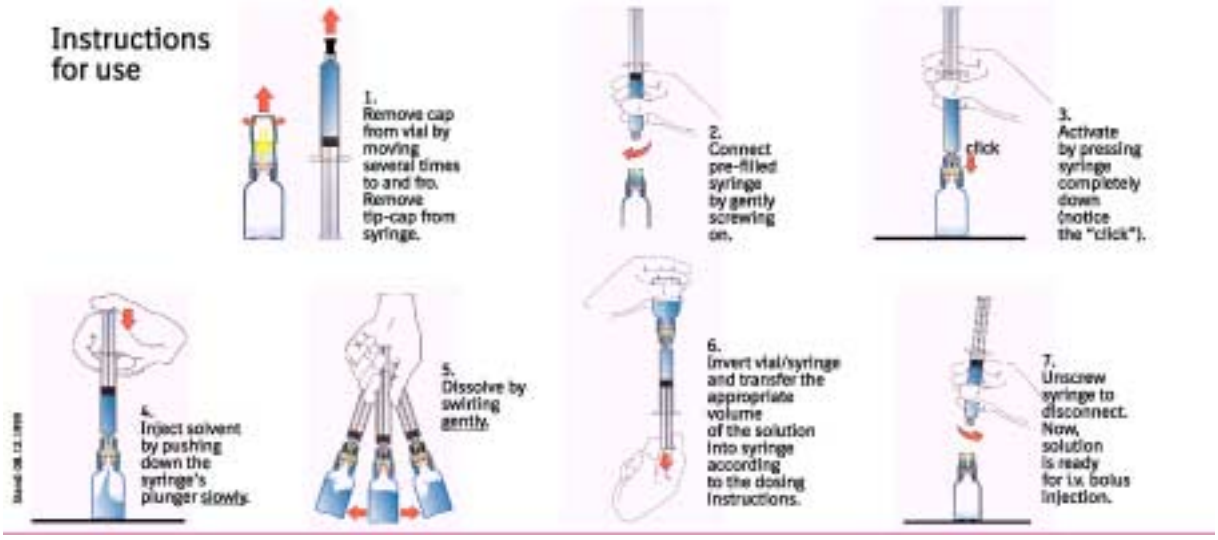
15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM

Step 3:
Place the vial on a firm surface and strongly press down the body of the syringe until an evident ***"click"*** is noticed. The ***"click"*** confirms the system is activated.

Below "Instructions for use"
Failure to complete step 3 correctly may lead to leakage of fluid and greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.



PARTICULARS TO APPEAR ON THE VIAL LABEL

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 8,000 U
Powder for solution for injection.
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

8,000 U tenecteplase per vial

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 8 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Read the package leaflet before use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for Tenecteplase Boehringer Ingelheim Pharma KG 8,000 U
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

Reconstituted solution, for patients of body weight (kg):

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 ml water for injections

PARTICULARS TO APPEAR ON THE CARTON LABEL.

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 10,000 U
Powder and solvent for solution for injection
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

10,000 U tenecteplase per vial

When reconstituted with 10 ml water for injections each ml contains 1,000 U tenecteplase

3. LIST OF EXCIPIENTS

Excipients: L-Arginine, Phosphoric Acid, Polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for injection
1 pre-filled syringe of solvent for parenteral use

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 10 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Please follow accurately the instructions for use. Failure to do so may lead to greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/168/003

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

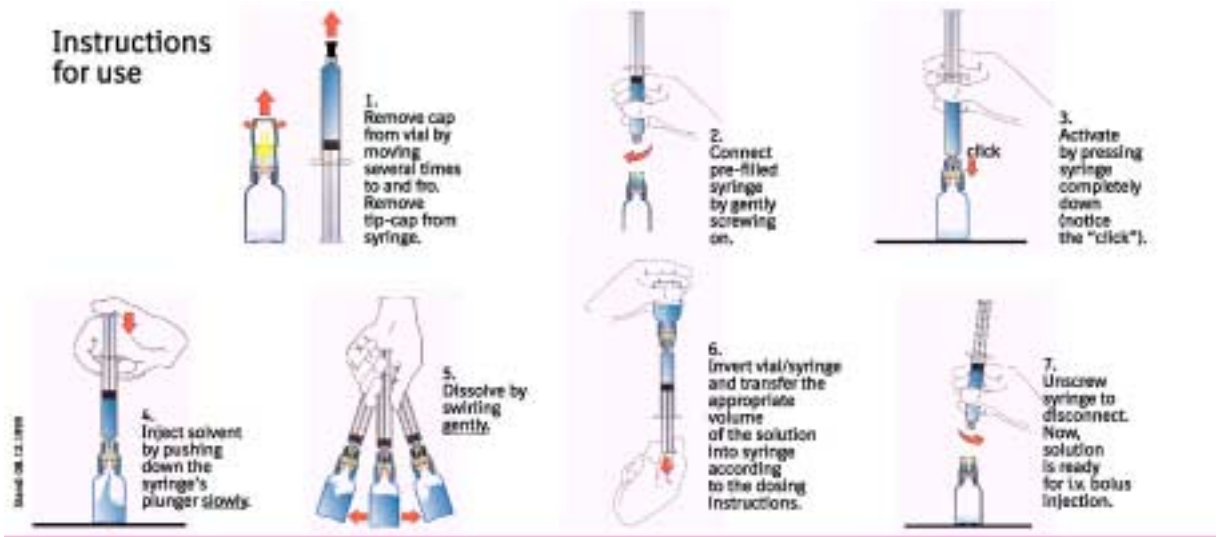
15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately. Any unused solution should be discarded. Only clear solution without particles should be used. Read the leaflet for information on reconstitution and dose to be administered.

PARTICULARS TO APPEAR ON THE INNER SIDE OF THE LID OF THE CARTON IN FORM OF A PICTOGRAMM

Step 3:
Place the vial on a firm surface and strongly press down the body of the syringe until an evident ***"click"*** is noticed. The ***"click"*** confirms the system is activated.

Below "Instructions for use"
Failure to complete step 3 correctly may lead to leakage of fluid and greater than the required dose of Tenecteplase Boehringer Ingelheim Pharma KG being administered.



PARTICULARS TO APPEAR ON THE VIAL LABEL

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tenecteplase Boehringer Ingelheim Pharma KG 10,000 U
Powder for solution for injection.
Tenecteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

10,000 U tenecteplase per vial

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution with 10 ml solvent

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Keep the container in the outer carton

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Read the package leaflet before use

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL FOR SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for Tenecteplase Boehringer Ingelheim Pharma KG 10,000 U
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

Reconstituted solution, for patients of body weight (kg):

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml water for injections